UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/426,340 | 10/25/1999 | THOMAS SANDAL | 5600.200-US | 1759 |

25908 7590 02/26/2002

NOVOZYMES NORTH AMERICA, INC.
C/O NOVO NORDISK OF NORTH AMERICA, INC.
405 LEXINGTON AVENUE, SUITE 6400
NEW YORK, NY 10174

| EXAMINER |
|---|
| JOHANNSEN, DIANA B |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | 18 |

DATE MAILED: 02/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/426,340 | SANDAL ET AL. | |
| | Examiner | Art Unit | |
| | Diana B. Johannsen | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-19,21-25 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21-25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *17* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on November 8, 2001 has been entered.

2. Claims 1, 2, 13, 21, 22, 24, and 27 have been amended. Claims 1-19, 21-25, and 27 are now pending. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Rejections - 35 USC § 112*

4. Claims 1-19, 21-25, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-19, 21-25, and 27 are indefinite over the recitation of the phrase "preparing a gene library directly from the enriched environmental pool of organisms" in claim 1 and the phrase "producing gene libraries directly from the enriched environmental pool of organisms" in claim 21. The language "preparing/producing

...directly" is vague and indefinite, because it is unclear as to how the inclusion of the term "directly" further limits the claims. For example, in what manner would "producing a gene library from" a pool or organisms differ from "producing a gene library directly" from that pool? It is clear from the teachings of the specification that a variety of steps are necessary to achieve gene library preparation (see, e.g., Example 3), and it is unclear as to what types of steps would be excluded by the language "directly" (i.e., when would the method become "indirect" as opposed to "direct"?). A clear and limiting definition of this language is not provided in either the specification or the art, such that one of skill would be apprised as to how the inclusion of the language "directly" would limit the methods of the claims.

Claims 21-24 are indefinite over the recitation of the phrase "method of selecting a DNA sequence encoding a polypeptide of interest," and for failing to recite a final process step that clearly relates back to the claim preamble. First, with respect to the language "method of selecting a DNA sequence of interest", etc., it is unclear as to what is meant by the language "selecting a DNA sequence". For example, does this language require, e.g., detection of a sequence, isolation of a molecule, etc.? Further, it is unclear as to whether this language might encompass solely mental steps of "selecting" a sequence. Second, it is noted that while the claims are drawn to a method 'of "selecting a DNA sequence....", the claims require a final process step of screening libraries "for DNA encoding the polypeptide of interest". It is unclear as to how the step of screening relates back to the preamble objective of "selecting". Further, it is unclear

as to whether the claims are intended to be drawn to a method of "selecting" or to a method of "screening". Clarification is required.

***Claim Rejections - 35 USC § 103***

5. Claims 1-7, 13-19, 21-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duvick et al (WO 96/06175 [2/1996]) in view of Sarkar and Upadhyay (Folia Microbiologica 38(1):29-32 [1993]).

Duvick et al teach methods for identifying organisms having a particular enzymatic activity (fumonisin degradation) by growing the organisms in media in which the enzyme substrate (fumonisin B1 or B2) is provided as the sole carbon source (p. 4-6, Example 1). The organisms employed in Duvick et al's methods are from "environmental pools" (e.g., seeds and stalks [see p. 4]). Duvick et al teach genomic libraries and disclose methods for preparing said genomic libraries from the nucleic acids of the microorganisms encoding the protein of interest (a fumonisin esterase) (p. 24-25). In particularly, Duvick et al state that "Microorganisms demonstrating fumonisin-resistance can be used to create a genomic library using standard techniques, well known in the art" (p. 24, lines 19-20). Furthermore, Duvick et al discloses screening libraries for genes encoding proteins having the ability to degrade a particular substrate (fumonisin), and disclose "selecting" such genes for further analysis (subcloning, sequencing, expression, etc.) (p. 25). Duvick et al do not teach the use in their methods of environmental pools of organisms isolated from the sources set forth in claims 1 and 21. Furthermore, Duvick et al do not teach employing their methods to prepare libraries

enriched in nucleic acids encoding a polypeptide "with an activity of interest" that acts on the substrates set forth in claim 4, and/or nucleic acids encoding enzymes of the types set forth in claims 16 or 27. Additionally, Duvick et al do not teach screening for genes encoding such polypeptides, as required by claim 24. Finally, Duvick et al do not teach employing growth conditions or "restrictions" such as those set forth in claim 7.

Sarkar and Upadhyay disclose that *Bacillus thermoalcaliphilus* isolated from an "the soil of a termite" produces a cellulase that is most stable at pH 8.5-9.5 and optimally active at 70°C (see entire reference, especially p. 29-30). Sarkar and Upadhyay teach growth of this bacterium in media comprising cellulose at 60°C, pH 8.5 (p. 29). In view of the teachings of Sarkar and Upadhyay, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Duvick et al so as to have prepared from a termite soil sample a genomic library enriched for a *B. thermoalcaliphilus* gene encoding the thermostable cellulase taught by Sarkar and Upadhyay, and so as to have screening or selected that gene for further analysis. An ordinary artisan would have been motivated to have made such a modification for the advantage of, e.g., rapidly isolating and sequencing the cellulase-encoding gene, rapidly preparing recombinant forms of the cellulase for additional study or use, etc. With respect to claim 4, it is further noted that Sarkar and Upadhyay disclose that cellulose is a substrate for cellulase, and teach growth of cellulase producing organisms in media comprising cellulose. With respect to claim 5, it is noted that Duvick et al teach enrichment of a pool of organism by the imposition of growth restrictions (growth in media in which the substrate of the desired

enzyme is the sole carbon source). With further reference to claim 6, it is noted that it is a property of the growth restrictions employed by Duvick et al and Sarkar and Upadhyay that they "comprise pH and temperature". With respect to claim 7, it is further noted that it would have been *prima facie* obvious to one of ordinary skill in the art to have selected the growth conditions taught by Sarkar and Upadhyay for use in the method of Duvick et al in view of Sarkar and Upadhyay in order to have assured optimal growth of the bacterium from which nucleic acids of interest were to be cloned, for the advantages of convenience and efficiency. With respect to claim 23, it is noted that Duvick et al disclose screening clones for an "active enzyme" ("their ability to degrade fumonisin" and selection of "colonies that degrade fumonisin" (p. 25)).

It is noted that in the Remarks of paper no. 16, Applicants traverse the rejection of claims 1-7, 13-19, 21-25 and 27 over Duvick et al in view of Sarkar and Uadhyay, as set forth in the Office action of paper no. 9. Applicants argue that the methods of Duvick et al require additional steps not required by the method of the instant claims; e.g., steps of "isolating positive organisms through several rounds of selection," "making a gene library from a selected organism," etc. Applicants argue that 'the specification does not....teach the step of preparing a gene library by first isolating a positive strain prior to producing the library," and state that "Duvick et al, alone or in combination with the other cited references, does not teach the step of preparing a gene library directly from the enriched pool." These arguments have been thoroughly considered but are not persuasive. The Duvick et al reference does not teach or suggest that one must perform additional steps of, e.g., "isolating organisms through several rounds of

selection" prior to preparing a library, as asserted by Applicants. Rather, as discussed above, the reference teaches growth of environmental samples in the presence of an enzyme substrate (fumonisin) in order to select organisms in a mixed population capable of degrading that substrate, and further teaches that "Microorganisms demonstrating fumonisin-resistance can be used to create a genomic library using standard techniques" (p. 24). The reference does not suggest that any further processing, screening, or selection of "microorganisms demonstrating fumonisin-resistance" is necessary prior to preparation of a genomic library. Rather, at pages 24-25, Duvick et al disclose that additional steps of the type discussed in applicants' remarks occur after library preparation. In particular, Duvick et al describe library preparation at lines 19-31 of page 24, and then at line 1 of page 25 state: "Once the cloning vector has been inserted into an appropriate host cell, the cells are grown on fumonisin containing media and screened for their ability to degrade fumonisin as previously described". The reference goes on to describe further steps of identifying complete coding sequences encoding fumonisin degrading enzymes, etc. (p. 25-26). However, these additional steps of screening for full length functional genes, etc., occur after the initial step of preparing a genomic library from "microorganisms demonstrating fumonisin-resistance". Accordingly, the steps of Duvick et al's methods correspond to those claimed by applicants. Further, the screening steps used by Duvick et al subsequent to library preparation are analogous to step c) of instant claim 21, in which libraries are screened "for DNA encoding the polypeptide of interest". As in Applicants' methods, these steps employed by Duvick et al are performed subsequent to library

preparation; the screening steps are not a part of library preparation, as asserted by Applicants. Further, Applicants' claims are sufficiently broad so as to encompass the performance of additional screening steps subsequent to library preparation, and in fact include such additional steps in, e.g., claim 21. Accordingly, Applicants arguments are not persuasive.

6. Claims 1-9, 13-19, 21-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duvick et al in view of Cotta (Appl. Environment. Microbiol. 54(3):772-776 [3/1988]).

Duvick et al teach methods for identifying organisms having a particular enzymatic activity (fumonisin degradation) by growing the organisms in media in which the enzyme substrate (fumonisin B1 or B2) is provided as the sole carbon source (p. 4-6, Example 1). The organisms employed in Duvick et al's methods are from "environmental pools" (e.g., seeds and stalks [see p. 4]). Duvick et al teach genomic libraries and disclose methods for preparing said genomic libraries from the nucleic acids of the microorganisms encoding the protein of interest (a fumonisin esterase) (p. 24-25). In particularly, Duvick et al state that "Microorganisms demonstrating fumonisin-resistance can be used to create a genomic library using standard techniques, well known in the art" (p. 24, lines 19-20). Furthermore, Duvick et al discloses screening libraries for genes encoding proteins having the ability to degrade a particular substrate (fumonisin), and disclose "selecting" such genes for further analysis (subcloning, sequencing, expression, etc.) (p. 25). Duvick et al do not teach the use in their methods of environmental pools of organisms isolated from the sources set forth in claims 1 and

21. Particularly, Duvick et al do not teach employing their methods to prepare libraries enriched in nucleic acids encoding a polypeptide of interest from an environmental pool "isolated from an animal stomach or an insect gut", as required by claim 8, or from a pool of microorganisms "isolated from a cow's rumen", as required by claim 9. Further, Duvick et al do not teach employing their methods to prepare libraries enriched in nucleic acids encoding a polypeptide "with an activity of interest" that acts on the substrates set forth in claim 4, and/or nucleic acids encoding enzymes of the types set forth in claims 16 or 27. Additionally, Duvick et al do not teach screening or "selecting" genes encoding such polypeptides, as required by claim 24.

Cotta teaches that several bacteria present in the rumen of cattle produce amylases that degrade starch (see entire reference). In view of the teachings of Cotta, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Duvick et al so as to have prepared from a sample of bacteria isolated from cattle rumen genomic libraries enriched for genes encoding the amylases taught by Cotta, and so as to have screened or "selected" such genes for further analysis. An ordinary artisan would have been motivated to have made such a modification for the advantage of, e.g., rapidly isolating and sequencing the amylase-encoding genes, rapidly preparing recombinant forms of the amylases for additional study or use, etc. With respect to claim 4, it is further noted that Cotta teaches that amylases degrade amylose (see, e.g., p. 773).

It is noted that in the Remarks of paper no. 16, Applicants traverse the rejection of claims 1-9, 13-19, 21-25 and 27 over Duvick et al in view of Cotta, as set forth in the

Office action of paper no. 9, for the same reasons set forth in paragraph 5, above. Accordingly, the response to those arguments set forth in paragraph 5, above, applies equally herein.

7. Claims 1- 8, 10, 12-19, 21-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duvick et al in view of Jacobsen and Schlein (J. Euk. Microbiol. 44(3):216-219 [1997]).

Duvick et al teach methods for identifying organisms having a particular enzymatic activity (fumonisin degradation) by growing the organisms in media in which the enzyme substrate (fumonisin B1 or B2) is provided as the sole carbon source (p. 4-6, Example 1). The organisms employed in Duvick et al's methods are from "environmental pools" (e.g., seeds and stalks [see p. 4]). Duvick et al teach genomic libraries and disclose methods for preparing said genomic libraries from the nucleic acids of the microorganisms encoding the protein of interest (a fumonisin esterase) (p. 24-25). In particularly, Duvick et al state that "Microorganisms demonstrating fumonisin-resistance can be used to create a genomic library using standard techniques, well known in the art" (p. 24, lines 19-20). Furthermore, Duvick et al discloses screening libraries for genes encoding proteins having the ability to degrade a particular substrate (fumonisin), and disclose "selecting" such genes for further analysis (subcloning, sequencing, expression, etc.) (p. 25). Duvick et al do not teach the use in their methods of environmental pools of organisms isolated from the sources set forth in claims 1 and 21. Particularly, Duvick et al do not teach employing their methods to prepare libraries enriched in nucleic acids encoding a polypeptide of interest from an environmental pool

"isolated from an animal stomach or an insect gut", as required by claim 8, or from "the gut of an insect of the *Isoptera, Lepidoptera, Coleoptera,* or *Diptera* families", as required by claim 10. Further, Duvick et al do not teach employing their methods to prepare libraries enriched in nucleic acids encoding a polypeptide "with an activity of interest" that acts on the substrates set forth in claim 4, and/or nucleic acids encoding enzymes of the types set forth in claims 16 or 27. With respect to claim 12, Duvick et al do not teach supplying a substrate in the feed of an animal or insect. Additionally, Duvick et al do not teach "selecting" genes encoding such polypeptides, as required by claim 24.

Jacobsen and Schlein teach that *Leishmania* present in the midgut of the sandfly *Phlebotomus papatasi* produce cellulases that degrade cellulose (see entire reference). In view of the teachings of Jacobsen and Schlein, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Duvick et al so as to have prepared from a sample of *Leishmania* isolated from sandfly midgut genomic libraries enriched for genes encoding the cellulases taught by Jacobsen and Schlein and so as to have "selected" such genes for further analysis. An ordinary artisan would have been motivated to have made such a modification for the advantage of, e.g., rapidly isolating and sequencing the cellulase-encoding genes, rapidly preparing recombinant forms of the cellulases for additional study or use, etc. With respect to claim 4, it is noted that Jacobsen and Schlein teaches that cellulases degrade cellulose (see, e.g., p. 216). With respect to claim 10, it is noted that *Phlebotomus papatasi* is a member of the order *Diptera*. With respect to claim 12,

it is noted that Jacobsen and Schlein suggest feeding flies with feed that comprises cellulose (p. 216).

It is noted that in the Remarks of paper no. 16, Applicants traverse the rejection of claims 1-8, 10, 12-19, 21-25 and 27 over Duvick et al in view of Jacobsen and Schlein, as set forth in the Office action of paper no. 9, for the same reasons set forth in paragraph 5, above. Accordingly, the response to those arguments set forth in paragraph 5, above, applies equally herein.

8. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Duvick et al in view of Jacobsen and Schlein, as applied to claims 1- 8, 10, 12-19, 21-25, and 27, above, and further in view of Siegle et al (US Patent No.4,027,037).

The combined references of Duvick et al and Jacobsen and Schlein do not teach preparing "enriched" gene libraries from microorganisms isolated from the guts of the insect species set forth in claim 11. It is noted that the instant claim is not limited to methods in which, e.g., a gene encoding a polypeptide having a particular activity in a particular species is identified or detected. Accordingly, the instant claim encompasses methods of preparing a library comprising any DNA "encoding a polypeptide with an activity of interest" from any pool of microorganisms isolated from the gut of any of the species set forth in the claim. Siegle et al teach a variety of orders and species of arthropods, including both *Phlebotomus* species and *Agrotis* species (col 6, line 32-col 7, line 38). In view of the teachings of Siegle et al, it would have been *prima facie* obvious at the time the invention was made to have modified the method of Duvick et al in view of Jacobsen and Schlein so as to have prepared enriched gene libraries from

nucleic acids of the gut bacteria of any of the arthropods taught by Siegle et al, including *Agrotis* species. An ordinary artisan would have been motivated to have made such a modification for the advantage of, e.g., rapidly isolating and sequencing a gene encoding any polypeptide of interest, rapidly preparing recombinant forms such a polypeptide for additional study or use, etc.

***Conclusion***

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

Diana B. Johannsen
February 20, 2002